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Name	Firm/Company	Fax Number	Phone Number
To: Examiner Daniel E. Kolker	United States Patent Office	571-273-3181	

From: Xuqiong Wu

Comments: Per your conversation with Xuqiong Wu, attached is Exhibit A to the Declaration.

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Submitted By: Xuqiong Wu	Phon :

nature

Porters South
4-6 Crinan Street
London N1 9XW
Tel: +44 (0)171 833 4000
Fax: +44 (0)171 843 4596/7
email: nature@nature.com

In reply please quote:
W12791 RD/rw

1 February 1999

Dr A Wellstein
Lombardi Cancer Center & Dept
of Pharmacology, Georgetown
University Medical Center
3970 Reservoir Road
Washington DC 20007

Dear Dr Wellstein,

Your manuscript "Anaplastic lymphoma kinase (ALK) is a receptor for the growth factor pleiotrophin" has now been seen by two referees whose comments are attached, and in the light of their advice I am sorry to say we are unable to offer to publish it in *Nature*.

You will see that, while they find your work interesting, they raise substantive concerns which cast doubt on the strength of the novel conclusions that can be drawn at this stage. We are therefore persuaded that the readers who will be most interested in your manuscript will be well-served by its publication in one of the many excellent journals specialising in the field.

With regret, we are therefore returning your manuscript in the hope that you find our referees' comments helpful when preparing it for resubmission elsewhere.

Yours sincerely,

Dr Ritu Dhand
Associate Editor

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The major claim of Aigner et al. (W12791) is that ALK is the receptor for PTN. The paper begins by describing a rather unconvincing experiment and does not markedly improve.

The first experiment described uses immoblized PTN to pan a phage display library, resulting in identification of a phage with a short sequence homolgous to ALK. Such a finding would be remarkable in that no one has previously been able to convincingly show that a short segment of any growth factor receptor will bind to its ligand when made in this manner, as such receptors need longer stretches that must be folded correctly (usually in mammalian expression systems) in order to bind their ligands. Since this technology does not generally work with known receptor/ligand pairs, it seems unlikely to have worked in this case. Yet the authors never go back to address or prove that such an unlikely situation worked in their benefit. They proceed to describe rather unconvincing binding studies that utilize no competition assays or true quantitation. Further, they never address the original phage finding via more classical binding experiments, for example by using deletion studies to show which region of ALK (presumably that corresponding to the phage sequence) is necessary to bind PTN. They then move on to perform rather unconvincing receptor phosphorylation assays. Though they claim it as "data not shown", they never depict studies of PTN inducing phosphorylation of endogenous Alk receptors. Instead, they only claim induced phosphorylation when the ALK receptor is transiently and ectopically overexpressed in COS cells. The latter study is very unconvincing since most receptor tyrosine kinases are constitutively phosphorylated when overexpressed in COS cells, even in the absence of ligand. Since basic technologies showing that receptors and ligands interact are so poorly exploited, far more controversial techniques using ribozymes cannot be believed. The final expression studies do not add much.

In summary, this paper is not of publishable quality for any journal, let alone Nature.

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